Prognostic value and function of KLF4 in prostate cancer: RNAa and vector-mediated overexpression identify KLF4 as an inhibitor of tumor cell growth and migration.

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Public Summary:
KLF4 is a transcriptional factor important for maintaining stem cell pluripotency and also a tumor suppressor in several types of cancer. In this study we found that KLF4 is significantly downregulated in prostate cancer cell lines and in prostate cancer tissues especially those with metastasis. RNAa mediated KLF4 activation in prostate cancer cells led to inhibited cell proliferation/survival and migration/invasion, and altered expression of several cell-cycle-related genes regulated by KLF4. These results could be recapitulated by vector-based KLF4 overexpression, validating RNAa as a method to restore gene expression and function.

Scientific Abstract:
KLF4/GLKF4 is a transcription factor that can have divergent functions in different malignancies. The role of KLF4 in prostate cancer etiology remains unclear. We have recently reported that small double-stranded RNA can induce gene expression by targeting promoter sequence in a phenomenon referred to as RNA activation (RNAa). In this study, we examine KLF4 levels in prostate cancer tissue and utilize RNAa as a tool for gene overexpression to investigate its function. Expression analysis indicated that KLF4 is significantly downregulated in prostate cancer cell lines compared with nontumorigenic prostate cells. Meta-analysis of existing cDNA microarray data also revealed that KLF4 is frequently depleted in prostate cancer tissue with more pronounced reduction in metastases. In support, tissue microarray analysis of tumors and patient-matched controls indicated downregulation of KLF4 in metastatic tumor samples. Logistic regression analysis found that tumors with a KLF4 staining score less than 5 had a 15-fold higher risk for developing metastatic prostate cancer (P = 0.001; 95% confidence interval, 3.0-79.0). In vitro analysis indicated that RNAa-mediated overexpression of KLF4 inhibited prostate cancer cell proliferation and survival and altered the expression of several downstream cell-cycle-related genes. Ectopic expression of KLF4 via viral transduction recapitulated the RNAa results, validating its inhibitory effects on cancer growth. Reactivation of KLF4 also suppressed migration and invasion of prostate cancer cells. These results suggest that KLF4 functions as an inhibitor of tumor cell growth and migration in prostate cancer and decreased expression has prognostic value for predicting prostate cancer metastasis.